REMARKS

Claims 29-35 were pending in the application. Claim 30 has been withdrawn, claims 31 and 32 have been canceled, claims 29 and 33 has been amended, and new claims 36-40 have been added. Accordingly, after the amendments presented herein have been entered, claims 29, 30, and 33-40 will be pending in the instant application. *No new matter has been added.*

Support for the amendments to the claims and for the new claims can be found throughout the specification and claims as originally filed. In particular, support for the amendment to claim 29 may be found at, for example, page 15, line 21 through page 16, line 4 of Applicants' specification. Support for new claims 38-40 may be found at, for example, page 9, lines 6-20 and page 32, line 11 of Applicants' specification. Support for new claim 37 may be found at, for example, page 8, lines 3-18 of Applicants' specification.

Cancellation of and/or amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application.

Election/Restrictions

The Examiner has stated that "Applicant's election with traverse of the species of IL-4 inducible promoter in the paper filed 11/03/2003 is acknowledged. The traversal is on the ground(s) that 'IL-4 inducible promoter' and 'inducible promoter' are not separate species because the IL-4 inducible promoter is a type of inducible promoter."

Applicants' gratefully acknowledge the Examiner's indication that "both the 'IL-4 inducible promoter' and 'inducible promoter' will be searched."

Rejection of Claims 29 and 31-35 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 29 and 31-35 under 35 U.S.C. §112, first paragraph,

> because the specification while being enabling for a retroviral vector comprising a fusion nucleic acid comprising: i) an IL-4 inducible epsilon promoter with the sequence as set forth as SEQ ID NO:1; ii) a first reporter gene; iii) a nucleic acid encoding a 2a site; and iv) a second reporter gene, does not reasonable provide enablement for a retroviral vector comprising a fusion nucleic acid comprising: i) an inducible promoter or an IL-4 inducible epsilon promoter; ii) a first reporter gene; iii) a nucleic acid encoding a 2a site; and iv) a second reporter gene.

In particular, the Examiner is of the opinion that "[t]he claims as written thus encompass all inducible promoters, while providing only one example, and the term IL-4 inducible promoter is defined in the specification as encompassing derivatives (see page 8, lines 24-25). Applicant only discloses an IL-4 inducible epsilon promoter of SEQ ID NO:1. Since the claims encompass variant nucleic acids, it would require undue experimentation to make and use the claimed invention." The Examiner is further of the opinion that

> [i]t would require undue experimentation for one of skill in the art to make and use the claimed polynucleotides, since the skilled artisan would have to first make the polynucleotide variants, but there is no functional limitation set forth for the claimed polynucleotide. Thus since Applicant has only taught how to test for polynucleotide variants, and has not taught how to make polynucleotide variants, it would require undue experimentation of one of skill in the art to make and use the claimed vectors.

Applicant respectfully submits that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation for the following reasons. Claim 29 is directed to a retroviral vector comprising a fusion nucleic acid comprising: i) a promoter of interest, ***wherein the promoter of interest is an IL-4 inducible ε promoter***; ii) a first reporter gene; and iii) a second reporter gene, wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site. Applicants respectfully submit that Applicants' specification teaches how to make and use the claimed ***IL-4 inducible ε promoters***. For example, at page 8, lines 3-18, provides a definition of an IL-4 inducible promoter as follows:

> ***[b]y "an IL-4 inducible promoter" herein is meant a nucleic acid promoter that is induced by IL-4, putatively by binding an unknown IL-4 induced DNA binding protein that results in induction of the promoter; that is, the introduction of IL-4 causes the pronounced activation of a particular DNA binding protein that then binds to the IL-4 inducible promoter segment and induces transcription***. The sequence of the human IL-4 inducible promoter is shown in Figure 1, and as will be appreciated by those in the art, derivatives or mutant promoters are included within this definition. Particularly included within the definition of an IL-4 inducible promoter are fragments or deletions of the sequence shown in Figure 1. (***Emphasis added***).

Therefore, contrary to the Examiner's assertion, Applicants' specification provides a description of an IL-4 inducible promoter, and functionally defines an IL-4 inducible promoter as set forth above. Therefore, the claimed invention is not directed to the genus of all inducible promoters, but rather ***only those promoters which are capable of being is induced by IL-4.*** One of ordinary skill in the art could make and use the claimed IL-4 inducible promoters, including IL-4 inducible promoters which are derivatives, mutants, or fragments of the

nucleotide sequence set forth as SEQ ID NO:1, without undue experimentation. The production of derivatives, mutants, or fragments of SEQ ID NO:1 was conventional in the art at the time the application was filed. Once produced, testing these derivatives, mutants, or fragments of SEQ ID NO:1 for functional activity as described in Applicants' specification, *i.e.,* the ability to be induced by IL-4, is taught in Applicants' specification and was also conventional in the art at the time the application was filed. In fact, the Examiner specifically states that Applicants' have taught how to test for polynucleotide variants.

It is Applicants' position that, given the guidance in Applicants' specification and the teachings in the art at the time the invention was made, one of ordinary skill in the art would be able to practice the invention as claimed using no more than routine experimentation. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 29 and 31-35 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 29 and 31-35 under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> the claims as written encompass all inducible promoters, while only providing one example, and the term IL-4 inducible promoter is defined in the specification as encompassing derivatives (see page 8, lines 24-25). Applicant only discloses an IL-4 inducible epsilon promoter of SEQ ID NO:1. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification do not place any limits on the number of substitutions, deletions, insertions

> and/or additions that may be make to the promoter. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. . . since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO:1 is insufficient to describe the genus.

Applicants respectfully traverse the foregoing rejection. Applicants' respectfully submit that the claimed invention does not encompass retroviral vectors comprising any and all inducible promoters. Rather, the claims as amended are limited to retroviral vectors comprising an IL-4 inducible promoter. Variant promoters which are encompassed by the claim are limited to variants which are capable of being induced by IL-4, and therefore contain distinguishing functional characteristics. An example of the sequence of an IL-4 inducible promoter is set forth in Applicants' specification. The identification or production of variant nucleic acid sequences was well-known in the art at the time the application was filed. Testing the variant promoters for the ability to be induced by IL-4 was also known to those of skill in the art. Thus, based on the teachings in Applicant's specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 29 and 31-35 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 29 and 31-35 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, the Examiner is of the opinion that "[c]laim 29 is vague and indefinite in the recitation of the term '2a site.' The sequence to which this term refers is not clear from the claim, and the specification does not clearly define it."

Applicants respectfully traverse the foregoing rejection and submit that the term "2a site" is clear and definite. Claim 29 has been amended such that it no longer recites the term "2a site." Claim 29, as amended, is directed to a retroviral vector comprising a fusion nucleic acid comprising: i) a promoter of interest, wherein the promoter of interest is an IL-4 inducible ε promoter; ii) a first reporter gene; and iii) a second reporter gene, wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site. New claim 36 has been added, which recites the term "2a site."

The Examiner has stated that Applicants' specification sets forth only that a 2a site is a protease cleavage site, "but does not give a sequence for it, or even a citation wherein the 2a site is defined." However, contrary to the Examiner's assertion, Applicants' specification at, for example page 15, line 21 through page 16, line 4, states that

> ***[i]n a preferred embodiment, when two reporter genes are used, they are fused together in such a way as to only require a single promoter, and thus some way of functionally separating the two genes is preferred. This can be done on the RNA level or the protein level.*** Preferred embodiments utilize either IRES sites (which allows the translation of two different genes on a single transcript (Kim, et al., "Construction of a Bifunctional mRNA in the Mouse By Using the Internal Ribosomal Entry Site of the Encephalomycarditis Virus," *Molecular and Cellular Biology* 12(8):3636-3643 (Aug 1992) and McBratney, et al., "The Sequence Context of the Initiation Codon in the Encephalomycarditis Virus Leader

> Modulates Efficiency of Internal Translation Initiation," *Current Opinion in Cell Biology* 5:961-965 (1993)), ***or a protease cleavage site (which cleaves a protein translation product into two proteins). Preferred protease cleavage sites include, but are not limited to, the 2a site (Ryan et al., J. Gen. Virol. 72:2727 (1991); Ryan et al., EMBO J. 13:928 (1994); Donnelly et al., J. Gen. Virol. 78:13 (1997); Hellen et al., Biochem, 28(26):9881 (1989); and Mattion et al., J. Virol. 70:8124 (1996), all of which are expressly incorporated by reference)." (Emphasis added).***

Therefore, Applicants' specification clearly provides several references which describe ***various*** examples of 2a sites. Furthermore, the term "2a site" was well-known to one of ordinary skill in the relevant art at the time the application was filed, as evidenced by the references cited in Applicants' specification.

As set forth in Applicants' specification, when two reporter genes are used, they are fused together in such a way as to only require a single promoter, and thus some way of functionally separating the two genes is preferred. This can be done on the RNA level or the protein level. This may be accomplished using a ***protease cleavage site, which cleaves a protein translation product into two proteins. Preferred protease cleavage sites include, but are not limited to, the 2a site.***

Moreover, Figure 11B-1 of Applicants' specification sets forth a nucleotide sequence representing an example of a vector of the invention, which includes a 2a cleavage sequence (at nucleotide residues 2895-2952). The claimed retroviral vectors are not limited to the sequence set forth in Figure 11B-1. However, this sequence provides an example of a nucleotide sequence encoding a 2a site.

Therefore, for the reasons set forth above, the term "2a site" is clear and definite and would be understood by one of ordinary skill in the art when read in combination with the

teachings of the specification taken as a whole. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

The Examiner is also of the opinion that "[c]laim 34 is vague and indefinite in the recitation of the term 'death gene.' There is no definition in the claim as to the gene this term encompasses and the specification (page 10, line 29 to page 11, line 18) provides non-limiting examples of what may be considered a death gene, but no definition is provided."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that Applicants' specification clearly sets forth what the term "death gene" encompasses. For example, Applicants' specification states that

> ***the reporter gene is a death gene that provides a nucleic acid that encodes a protein that causes the cells to die***. Death genes fall into two basic categories: death genes that encode death proteins that require a death ligand to kill the cells, and death genes that encode death proteins that kill cells as a result of high expression within the cell, and do not require the addition of any death ligand. It is preferable that cell death requires a two-step process: the expression of the death gene and induction of the death phenotype with a signal or ligand, such that the cells may be grown up expressing the death gene, and then induced to die. A number of death genes/ligand pairs are known, including, but not limited to, the Fas receptor and Fas ligand (Bodmer, et al., "Characterization of Fas," *J Biol Chem* 272(30):18827-18833 (Jul 25, 1997); muFAS, Gonzalez-Cuadrado, et al., "Agonistic anti-Fas Antibodies Induce Glomerular Cell Apoptosis in Mice In Vivo," *Kidney Int* 51(6):1739-1746 (Jun 1997); Muruva, et al., *Hum Gene Ther*, 8(8):955 (May 1997)), (or anti-Fas receptor antibodies); p450 and cyclophosphamide (Chen, et al., "Potentiation of Cytochrome P450/Cyclophosphamide-Based Cancer Gene Therapy By Coexpression of the P450 Reductase Gene," *Cancer Res* 57(21):4830-4837 (Nov 1 1997)); thymidine kinase and gangcylovir (Stone, R., "Molecular 'Surgery' For Brain Tumors," 256(5063):1513 (June 12, 1992)), tumor necrosis factor (TNF) receptor and TNF. Alternatively, the death gene need not require a ligand, and death results from high expression of the gene; for example, the overexpression of a number of programmed cell death (PCD) proteins are known to cause cell

> death, including, but not limited to, caspases, bax, TRADD, FADD, SCK, MEK, etc. (page 10, line 29 through page 11, line 19).

Therefore, based on the above, a "death gene" includes ***any*** nucleic acid that encodes a protein that causes the cells to die. As the Examiner is aware, breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). Furthermore, based on the references cited in Applicants' specification which provide examples of death genes, the term "death gene" was well-known in the art at the time the application was filed. Therefore, the term would be understood by one of ordinary skill in the art when read in combination with the teachings of the specification taken as a whole. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 29, 31, and 35 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 29, 31, and 35 under 35 U.S.C. §102(b), "as being anticipated by Iida et al (1996)." In particular, the Examiner is of the opinion that Iida et al

> [t]eaches a retroviral vector for delivery of genes into cells (see page 6054, column 2, first paragraph). The retroviral vectors of Iida, *et al.* comprise an inducible promoter of interest (the minimal CMV immediate early gene promoter), a first reporter gene (the CAT gene), a second reporter gene, which is a drug resistance gene (the neo gene) (see page 6055, Figure 1). The retroviral vector of Iida et al. anticipates all the limitations of the claims, because, as set forth in the rejection under 35 USC 112 second paragraph, supra, the limitation wherein the retroviral vector comprises a 2a sequence is vague and indefinite. Additionally, the encoded proteins would be able to be cleaved by a protease, which is the only indication in the Specification as to the identity of a 2a site, thus it is inherent that the sequences in the vector would encode a protease cleavage site.

Applicants respectfully traverse the foregoing rejection for the following reasons. For a prior art reference to anticipate a claimed invention, the prior art must teach each and every element of

the claimed invention. *Lewmar Marine v. Barient* 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 29 is directed to a retroviral vector comprising a fusion nucleic acid comprising: i) a promoter of interest, ***wherein the promoter of interest is an IL-4 inducible ε promoter***; ii) a first reporter gene; and iii) a second reporter gene, ***wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site***.

Iida, *et al.* describes a modified tetracycline-controlled inducible system in which the ligand-binding domain of the estrogen receptor (ER) is fused to the carboxy terminus of the tTA transactivator (referred to as the tTAER gene). To express this gene, a bicistronic retroviral vector, referred to as pTEPN, in which the tTAER gene was followed by the internal ribosome entry site derived from the poliovirus genome (PO) and the neomycin phosphotransferase (*neoR)* gene was constructed, and is shown in Figure 1 of the Iida, *et al.* reference (see page 6055, second column).

Iida *et al.* do not teach each and every limitation of the claimed invention. Iida *et al.* fail to teach or suggest a retroviral vector comprising a promoter of interest, ***wherein the promoter of interest is an IL-4 inducible ε promoter,*** as is set forth in claim 29. The only promoter described in Iida *et al.* which is used in the retroviral vectors described therein is tetO, a minimal CMV immediate-early gene promoter linked to seven tandem copies of the tetR binding site (see the description of Figure 1 at page 6055 of Iida *et al.*). In fact, the Examiner states at page 8 of

the instant Office Action that "Iida et al. does not teach the retroviral vector comprising an IL-4 inducible promoter." (see Page 8, lines 4-5 of the Office Action).

Furthermore, Iida *et al.* do not teach or suggest a retroviral vector comprising an IL-4 inducible promoter and ***two reporter genes, wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site.*** Nowhere does Iida *et al.* teach or suggest two reporter genes which are functionally separated. Furthermore, the plasmids described in Iida, *et al.* (see Figure 1), do not comprise two reporter genes which are fused, resulting in a single transcript.

The Examiner states that "the encoded proteins would be able to be cleaved by a protease." However, the Examiner provides no evidence of this, and Iida *et al.* do not teach or suggest ***a site which allows for functional separation of two reporter genes, wherein the site is a protease cleavage site.***

Furthermore, Iida *et al.* does not teach or suggest a 2a site, which, as set forth in Applicants' specification, is "a protease cleavage site (***which cleaves a protein translation product into two proteins***)," (see page 16, lines 1-4).

For the reasons set forth above, Iida *et al.* fail to teach each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 29 and 31-35 Under 35 U.S.C. §103

The Examiner has rejected claims 29 and 31-35 under 35 U.S.C. §103 "as being unpatentable over Iida *et al.* (1996) in view of Mikita *et al.* (1996), further in view of Persons et al. (1997), and further in view of U.S. Patent No. 5,834,266 (Crabtree et al) In particular, the Examiner is of the opinion that

> Iida et al.. . . . teaches a retroviral vector for delivery of genes into cells (see page 6054, column 2, first paragraph). The retroviral vectors of Iida, *et al.* comprise an inducible promoter of interest (the minimal CMV immediate early gene promoter), a first reporter gene (the CAT gene), a second reporter gene, which is a drug resistance gene (the neo gene) (see page 6055, Figure 1). It is an expected property of the retroviral vectors Iida et al. that the encoded proteins would be able to be cleaved by a protease, which is the only indication in the Specification as to the identity of a 2a site. Iida et al does not teach the retroviral vector comprising an IL-4 inducible promoter, a GFP gene, or a death gene.
>
> Mikita et al. teaches that Interleukin-4 (IL-4) stimulation leads to the activation of the signal transducer and activator of transcription 6 (STAT 6). Mikita et al studied the functional properties of STAT6. Mikita et al. cotransfected HEK 293 cells with a reporter construct comprising the IL-4 regulatory element, which is within the immunoglobulin heavy-chain epsilon promoter and expression vectors encoding mutant STAT6 proteins (see page 5815, Figure 4C). Thus Mikita et al. teaches the IL-4 inducible promoter in a vector. Neither Iida nor Mikita teach a retroviral vector comprising a sequence encoding a fluorescent protein. Persons et al. teaches a retroviral vector comprising the GFP gene. Neither Iida, Mikita not Persons teach a reporter gene which is a death gene. Crabtree et al. (column 133, claim 210) discloses the use of a genetic construct which is a retroviral vector. Crabtree et al. (column 129, claim 129) further discloses a method of producing a cell which is selectively killed in response to ligand binding, wherein the cell comprises a genetic construct comprising a ligand binding domain, which dimerizes upon ligand binding, and an action domain, which is the intracellular portion of Fas receptor. Also disclosed is the use of another apoptosis inducing genetic construct wherein the action domain comprises the TNF receptor.

Applicants respectfully traverse the foregoing rejection for the following reasons. To establish a *prima facie* case of obviousness for the claimed invention, there must have been some

suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

As set forth above, Iida, *et al.* describes a modified tetracycline-controlled inducible system in which the ligand-binding domain of the estrogen receptor (ER) is fused to the carboxy terminus of the tTA transactivator (referred to as the tTAER gene). To express this gene, a bicistronic retroviral vector, referred to as pTEPN, in which the tTAER gene was followed by the internal ribosome entry site derived from the poliovirus genome (PO) and the neomycin phosphotransferase (*neoR)* gene was constructed, and is shown in Figure 1 of the Iida, *et al.* reference (see page 6055, second column).

Iida *et al.* do not teach each and every limitation of the claimed invention. Iida *et al.* fail to teach or suggest a retroviral vector comprising a promoter of interest, ***wherein the promoter of interest is an IL-4 inducible ε promoter,*** as is set forth in claim 29. The only promoter described in Iida *et al.* which is used in the retroviral vectors described therein is tetO, a minimal CMV immediate-early gene promoter linked to seven tandem copies of the tetR binding site (see the description of Figure 1 at page 6055 of Iida *et al.*). In fact, the Examiner states at page 8 of

the instant Office Action that "Iida et al. does not teach the retroviral vector comprising an IL-4 inducible promoter." (see Page 8, lines 4-5 of the Office Action).

Furthermore, Iida *et al.* do not teach or suggest a retroviral vector comprising an IL-4 inducible promoter and two reporter genes, ***wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site.*** The plasmids described in Iida, *et al.* (see Figure 1), do not comprise ***two reporter genes which are fused***, resulting in a ***single transcript***. Furthermore, nowhere does Iida *et al.* teach or suggest two reporter genes which are ***functionally separated*** by a protease cleavage site.

The Examiner states that "the encoded proteins would be able to be cleaved by a protease." However, the Examiner provides no evidence of this, and Iida *et al.* do not teach or suggest ***a site which allows for functional separation of two reporter genes***. Furthermore, Iida *et al.* does not teach or suggest a 2a site, which, as set forth in Applicants' specification, is "***which cleaves a protein translation product into two proteins***," (see page 16, lines 1-4).

The secondary references of Mikita, *et al.*, Persons *et al.*, and Crabtree *et al.* fail to make up for the deficiencies of the Iida, *et al.* reference.

Mikita, *et al.* presents data relating to the functional properties of Stat6 and discloses that Interleukin-4 (IL-4) stimulation leads to the activation of Stat6. Mikita *et al.* also examined whether recombinant Stat6 protein could be activated in 293 cells in response to IL-4 and investigated whether the exogenously supplied protein could activate an IL-4 responsive reporter construct (page 5813, second column).

Mikita, *et al.* fail to teach or suggest each and every limitation of the claimed invention. Mikita *et al.* do not teach or suggest use of a ***retroviral*** vector. Retroviral vectors have several properties which distinguish them from other expression systems. For example, retroviral vectors integrate DNA into the host genome and allow for stable expression of the DNA in the cell. Mikita *et al.* describe ***transient*** expression of Stat6 in cells. Retroviral vectors were well-known in the art and available at the time Mikita *et al.* was published. However, Mikita *et al.* chose not to utilize these retroviral vectors in these experiments.

Furthermore, Mikita *et al.* do not teach or suggest a vector comprising a promoter and ***two reporter genes.*** Moreover, Mikita *et al.* also do not teach or suggest a retroviral vector comprising a promoter which is operably linked to the first reporter gene and the ***first and second reporter genes are fused***, resulting in a ***single transcript***. Furthermore, nowhere does Mikita *et al.* teach or suggest two reporter genes which are ***functionally separated*** by a protease cleavage site.

Persons *et al.* fail to cure the deficiencies of the Iida *et al.* reference. Persons *et al.* simply investigates the use of the green fluorescent protein (GFP) as a marker to assess retroviral gene transfer into hematopoietic cells and as a tool to identify and enrich for cells expressing high levels of the vector-encoded transcript. Persons *et al.* fail to teach or suggest a vector comprising an IL-4 inducible ε promoter. Furthermore, Persons *et al.* also fail to teach or suggest a vector comprising an IL-4 inducible ε promoter wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site.

Crabtree *et al.* also fail to cure the deficiencies of Iida *et al.* Crabtree *et al.* teach methods for the genetic engineering of vectors comprising a chimeric protein which may be used to render host cells and their progeny susceptible, in a regulated fashion, to programmed cell death (apoptosis). Crabtree *et al.* also fail to teach or suggest a vector comprising an IL-4 inducible ε promoter. Furthermore, Crabtree *et al.* also fail to teach or suggest a vector comprising an IL-4 inducible ε promoter wherein the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, wherein the site is a protease cleavage site.

Furthermore, the Examiner has stated that

> [t]he motivation and expectation of success is provided in Mikita *et al.* which teaches the importance of elucidating the mechanism governing IL-4 induced gene expression) Mikita at 5812, first column, second paragraph), Persons et al. which teaches that GFP can serve as an excellent marker of gene transfer in hemotopoietic tissues, and its utilization will allow purification of genetically modified cells ex vivo and the tracking of such cells following transplantation (see Persons et al. at 1785, column 1, fourth paragraph), and Crabtree et al. which discloses that the use of death domain as a reporter is a generally applicable method and can be used for utilizing protein homodimerization, heterodimerization and oligomerization in living cells.

Even if the cited art taught all the claim limitations, which Applicants deny, Applicants maintain that at the time the invention was made, the prior art failed to provide sufficient motivation to modify the teachings of the primary references to arrive at the claimed invention. With respect to motivation to make the claimed invention, the Examiner has failed to set forth adequate evidence of a motivating force which would have ***impelled*** one of ordinary skill in the art to modify the teachings of the references to arrive at the claimed invention.

Applicants respectfully submit that Mikita *et al.* fails to provide motivation which would have impelled one of ordinary skill in the art to create the claimed retroviral vectors of the invention. In particular, Mikita *et al.* is directed to the characterization of Stat6 and the role of Stat 6 in mediating the reprogramming of gene expression in response to IL-4. Iida *et al.* describes a modified tetracycline-regulated system. Even if these references disclosed each and every element of the claimed invention, which they do not, the mere recitation of separate elements of the claimed invention, in separate references, is not enough to provide motivation to combine these references. Furthermore, the cited art provide no motivation to combine the elements in such a way as to produce the presently claimed retroviral vector, *i.e.*, a retroviral vector which comprises an IL-4 inducible promoter and two reporter genes, ***where the promoter is operably linked to the first reporter gene and the first and second reporter genes are fused, such that transcription from the promoter results in a single transcript encoding the first and second reporter genes, and further comprising a site which allows for functional separation of the two reporter genes, where the site is a protease cleavage site.***

In support of their position, Applicants point to the CAFC decision in *In re Rouffet*, (149 F.3d 1350) (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Satellite Communications System" (Ruddy). The CAFC found that:

> [although] the board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's

> application. . .the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the Board did not identify any motivation to choose these references for combination.

Similarly, it is Applicants' position that the Examiner has failed to point to any motivation produce the claimed retroviral vectors. In *Rouffet* the Court of Appeals continued:

> [b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. *In re Rouffet* at [*17].

Since the Examiner has not pointed to any teaching or suggestion in the art that would have impelled the ordinarily skilled artisan to modify the cited art to arrive at the claimed retroviral vector, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.' " *SmithKline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

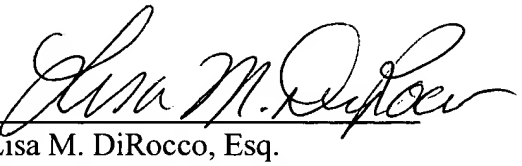
In view of the foregoing, Applicants respectfully submit that the combination of Iida *et al.* with Mikita *et al.,* Persons et al., and U.S. Patent No. 5,834,266 do not teach or suggest Applicants' invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: 

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